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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/083,817	02/26/2002	George F. Schreiner	SCIOS.002C1	8504

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EXAMINER	
SAOUD, CHRISTINE J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 08/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/083,817	SCHREINER ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Notice of Allowance, mailed 25 October 2004, is rescinded and prosecution is being reopened to add a new ground of rejection. Any delay in prosecution is regretted.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 25 January 2005 was filed after the mailing date of the Notice of Allowance on 25 October 2004, and contains the proper certification and fee. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131

USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation of elevated blood pressure, and the claim also recites hypertension which is the narrower statement of the range/limitation.

For clarity, claim 1 is directed to a method of treating hypertension, however, a patient with "an elevated blood pressure" is not necessarily a patient with hypertension. Hypertension is defined as a mean arterial pressure that is greater than the upper range of accepted normality (see Guyton, page 209, column 1, final paragraph – newly cited). Therefore, the claim is indefinite because it is not clear that hypertension is being treated if the patient does not have hypertension or if the claim is merely directed to reducing an "elevated" blood pressure.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites that the patient has "an elevated blood pressure", however, the metes and bounds of what is to be considered "elevated" are not clear because there is no point of reference with which to determine if a blood pressure would be considered elevated. Because hypertension has a known definition in the art, it is suggested that the claim be directed to a method of treating hypertension comprising administering to a patient having hypertension ... such that the blood pressure is reduced.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Hariawala et al. (J. Surg. Research 63: 77-82, 1996).

The instant claims are directed to a method of treating hypertension by administration of an effective amount of VEGF to a patient with an elevated blood pressure such that the elevated blood pressure is reduced.

Bania et al. administer VEGF to a patient (pig) which has been subjected to occlusion of the proximal circumflex coronary artery. The claims do not require that the patients have hypertension, only "an elevated blood pressure", nor do they require any particular amount of VEGF be administered or require any particular administration route. The pigs used by Hariwala et al. would reasonably be expected to have "an elevated blood pressure" because animals which are under research conditions frequently have a blood pressure above what would be found in an animal in its natural environment. Hariwala et al. teach at page 80, column 1, paragraph 1 that mean arterial blood pressure was significantly reduced by administration of VEGF. Hariwala et al. do not disclose if filtration or excretion of a solute is improved, but this would be an inherent property of the administration of the VEGF. Therefore, Hariwala et al. meets the limitations of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guyton (Textbook of Medical Physiology, 8th edition, W.B. Saunders Company, pages 209-218, 1991) in view of Roberts et al. (J. Cell Sci. 108: 2369-2379, 1995).

Guyton teaches that hypertension is a condition in which a person's arterial blood pressure is greater than the upper range of accepted normality. Hypertension can be caused by a number of different factors, including reduced renal mass, primary aldosteronism, secretion of renin by a renin-secreting tumor, coarctation of the aorta, patchy ischemic kidney disease, toxemia of pregnancy, neurogenic hypertention. Hypertension can also occur in individuals with no known origin for the hypertension, which is called essential hypertension. In individuals with essential hypertension, the "kidneys will not excrete adequate amounts of salt and water unless the arterial pressure is high" (see page 217, column 2, item #7). Essential hypertension is generally treated by giving drugs that (1) increase renal blood flow and/or (2) decrease tubular reabsorption of salt and water (see page 218, column 1, paragraph 2). Guyton does not teach the administration of VEGF such that renal filtration or excretion of a solute in the kidney is improved.

Roberts et al. teach that VEGF is a growth factor which has mitogenic effects on endothelium and occurs as 4 isoforms (121, 165, 189 and 206 amino acids). Roberts et al. also teach that VEGF induces endothelial fenestrae and increases vascular permeability to solutes. Roberts et al. also teach that fenestrated endothelium normally occurs in the capillaries of kidney glomeruli and that fenestrated capillary endothelium is more permeable to water and small solutes than continuous endothelium.

It would have been *prima facie* obvious at the time the instant invention was made to treat individuals with hypertension with VEGF in order to increase the excretion of salt and water in said individuals because Guyton teaches that individuals with essential hypertension have an impaired ability to excrete salt and water and because Roberts et al. teach that VEGF functions to increase the permeability of endothelium and that the kidney glomeruli have fenestrated endothelium. One would have a reasonable expectation of success because Roberts et al. teach that fenestrated capillary endothelium is more permeable to small solutes and VEGF would stimulate fenestration of this tissue. Therefore, the invention as a whole would have been *prima facie* obvious at the time the invention was made, absent evidence to the contrary.

Claims 1 and 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guyton (Textbook of Medical Physiology, 8th edition, W.B. Saunders Company, pages 209-218, 1991) in view of Hariawala et al. (J. Surg. Research 63: 77-82, 1996) further in view of Zioncheck et al. (U.S. Pat. No. 56,485,942).

The disclosure of Guyton is provided above. Guyton does not teach a method of treating hypertension with VEGF or VEGF121 or VEGF with a modified heparin binding domain.

Hariawala et al. teach that administration of VEGF reduces mean arterial blood pressure (see page 80, column 1, paragraph 1). Hariawala et al. also teach that VEGF causes significant vasodilation and hypotension. Hariawala et al. do not teach VEGF121 or VEGF with a modified heparin binding domain.

Zioncheck et al. teach that VEGF if expressed in a variety of tissues as multiple homodimeric forms (VEGF121, VEGF165, VEGF189 and VEGF206) resulting from alternative RNA splicing (see column 2, paragraph 2). VEGF contains a C-terminal heparin binding domain that spans the C-terminus and begins at about amino acid 120 (column 2, paragraph 3). VEGF121 is soluble and does not bind heparin and the longer forms of VEGF bind heparin with progressively higher affinity. Zioncheck et al. teach that alterations of the C-terminal heparin binding domain can reduce the affinity of VEGF for heparin, resulting in slower rates of clearance and smaller volumns of distribution. The effect of this is that less VEGF is cleared by non-specific target organs such as the liver.

It would have been *prima facie* obvious at the time the instant invention was made to treat individuals with hypertension with VEGF, including VEGF121 or VEGF molecules with an altered heparin binding domain, in order to decrease the blood pressure in said individuals because Guyton teaches that individuals with hypertension have an increased blood pressure and because Hariawala et al. teach that VEGF

administration causes vasodilation which decreases blood pressure. It also would have been prima facie obvious to practice this method of treating hypertension with VEGF121 or a form of VEGF with a modified heparin binding domain because Zioncheck et al. teach that these forms of VEGF either do not bind heparin or bind it at a lower affinity, resulting in a VEGF which has a slower rate of clearance from the body. One would be motivated to use the VEGF molecules of Zioncheck et al. because a VEGF molecule with a slower rate of clearance would require a smaller dose to maintain a biological effect because it would stay in the body longer. Additionally, one of ordinary skill in the art would be motivated to use more than one type of VEGF because therapeutics are often used where different forms with different clearance rates are desirable, resulting in a bolus dose and a maintenance effect. Therefore, the invention as a whole would have been *prima facie* obvious at the time the invention was made, absent evidence to the contrary.

Claims 1 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guyton (Textbook of Medical Physiology, 8th edition, W.B. Saunders Company, pages 209-218, 1991) in view of Hariawala et al. (J. Surg. Research 63: 77-82, 1996) further in view of Cid et al. (U.S. Pat. No. 5,318,957).

The disclosures of Guyton and Hariawala et al. are as provided above. Neither reference teaches coadministration of VEGF with another angiogenic factor.

Guyton teaches at page 209, column 2, that hypertension can lead to disorders such as congestive heart disease, coronary heart disease, cerebral infarct, as well as hemorrhages in the kidneys which can cause renal destruction. Cid et al. teach that

angiogenic factors stimulate the formation new blood vessels and that these factors are useful for treatment of conditions involving angiogenesis, such as myocardial and cerebral infarctions, limb ischemia, wounds and vascular occlusion or stenosis. It would have been prima facie obvious at the time the invention was made to treat individuals experiencing hypertension with VEGF in order to increase the excretion of salt and water in said individuals because Guyton teaches that individuals with hypertension have an impaired ability to excrete salt and water and because Hariawala et al. teach that VEGF causes vasodilation and decreases blood pressure. It also would have been *prima facie* obvious at the time of the instant invention to additionally administer an angiogenic factor in combination with VEGF because Cid et al. teach that angiogenic factors are useful for treatment of conditions which involve angiogenesis, and Guyton teach that hypertension can cause a number of conditions which involved angiogenesis. One would have been motivated to administer an angiogenic factor in combination with VEGF because Guyton teaches that secondary diseases/disorders can be caused by hypertension and because Cid et al. teach that administration of angiogenic factors would be beneficial for treatment of these conditions. One would have a reasonable expectation of success because Hariawala et al. teach that VEGF causes vasodilation and decreases blood pressure and Cid et al. teach that angiogenic factors stimulate formation of blood vessels which would be desireable in diseases related to hypertension. Therefore, the invention as a whole would have been *prima facie* obvious at the time the invention was made, absent evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 10/749,706. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both directed to treatment of hypertension by the administration of VEGF. The base claims differ in wording, but the patient population which is being treated is the same and the same protein is being administered, therefore, the claims are not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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